Bone morphogenetic protein-2 and -6 heterodimer illustrates the nature of ligand-receptor assembly.

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Public Summary:
TGF-beta superfamily ligands are homo- or heterodimeric protein molecules in the body and they recruit two membrane surface receptors known as type I and two type II kinase receptors. By binding to these receptors, the ligand proteins initiate a signaling cascade across the cell membrane. Even with the known three-dimensional atomic structure of the ligands in complex with cell-surface domains of these type I and type II receptors, it was unclear why the binding to these two types of receptors is sequential, meaning binding of one type (e.g. type II) is a prerequisite to recruit and bind the other type (e.g. type I). We generated a bone morphogenetic protein known as BMP-2/6 heterodimer. BMP-2/6 carries two asymmetric interfaces for each receptor type (type I and type II). We demonstrate that the BMP-2/6 possesses high affinity to both receptor types and increased cellular signaling activity when we characterized its property by cell-based chondrogenesis assays. Furthermore, we find that the minimal signaling complex actually consists of two type II receptors and one type I receptor bound to each ligand (e.g. BMP-2/6). Our study reveals how the protein-engineered BMP-2/6 may use their independent binding interfaces to differentially recruit the two different receptors. As a result, BMP-2/6 may generate new biological properties.

Scientific Abstract:
TGF-beta superfamily ligands are homo- or heterodimeric and recruit two type I and two type II Ser/Thr kinase receptors to initiate a transmembrane signaling cascade. Even with the known structure of the homodimer ligands in complex with extracellular domains of both receptor types, the sequential assembly of the signaling complex with its cognate receptors in the cell membrane remains elusive. We generated a bone morphogenetic protein-2/-6 heterodimer carrying two asymmetric interfaces for each receptor type. We demonstrate that the heterodimer possesses high affinity to both receptor types and increased Smad1-dependent signaling activity by both cell-based and chondrogenesis assays. Furthermore, we find that the minimal signaling complex consists of two type II receptors and one type I receptor per dimer. Our study reveals how the engineered heterodimers may use their independent binding interfaces to differentially recruit the different receptors for each receptor type to create new biological properties.